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(54) Title: CYCLOOXYGENASE-2 INHIBITORS

(57) Abstract: Use of compounds of formula (I) or salts thereof for the preparation of COX-2 inhibitor drugs: $R\text{-}T_1\text{-}B\text{-}C_{c0}\text{-}N(O)_s$ (formula I), for the treatment and/or prophylaxis of inflammatory processes.

TITLE OF THE INVENTION

"CYCLOOXYGENASE-2 INHIBITORS"

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The present invention relates to compounds able to inhibit selectively the enzyme COX-2 without inhibiting substantially the enzyme COX-1.

Specifically the present invention concerns nitroxyderivatives of non-steroidal anti-inflammatory compounds, which are able to inhibit selectively the enzyme COX-2.

It is well known that non-steroidal anti-inflammatory drugs are widely used as analgesics, antipyretics and in the treatment of pathologies that have an inflammatory origin. As known, the use of NSAIDs is limited by serious side-effects at gastrointestinal and renal levels and by haemorrhagic complications that appear after prolonged treatments with these drugs.

The inflammatory process originates from the activation of two isoforms of the enzyme cyclooxygenase (COX), which are involved in the activation of a series of biochemical processes, known as arachidonic acid cascade. In this series of biochemical processes the formation of metabolites, such as for example pro-algogenic and inflammatory prostaglandins and leukotrienes, takes place. The two isoforms of the enzyme cyclooxygenase are identified as cyclooxygenase-1 or COX-1 and cyclooxygenase-2 or COX-2 respectively (Annu. Rev. Pharmacol. Toxicol. 1998 38, 97-120). The COX-1 constitutively expressed in gastrointestinal, renal tissues or at endothelial level, plays a primary role in physiological phenomena, and at gastric mucosa level promotes the formation of the protective prostanoids involved in the gastric cytoprotection. The COX-2 produced after inflammatory stimuli represents the form of the enzyme cyclooxygenase responsible for the production of inflammatory and pro-algogenic prostanoids. Moreover, the COX-2 activates a series of factors that maintain and amplify the inflammatory process.

The NSAIDs present on the market inhibit both the isoforms, both the COX-1 and COX-2, provoking a decrease in the production of protective prostanoids, and therefore the appearance of the aforementioned side-effects. In order to obviate these inconveniences, drugs that inhibit selectively COX-2 without inhibiting substantially COX-1 have been proposed. Among the COX-2 inhibitor drugs, celecoxib, rofecoxib,

etc., can be mentioned. (Drugs of Future 1998, 23 (12) 1287-1296). It has been found that the use of these drugs is not exempt from side-effects, in particular those affecting gastrointestinal (Gastroenterology 1997, 112, 645-648), renal levels and above all those concerning the cardiovascular apparatus (JAMA 2001; 286, 954-959). Especially for what concerns the side-effects at gastrointestinal level, the delay that these drugs cause in the cicatrisation of pre-existent gastric ulcers, can be mentioned. Furthermore, in the presence of gastritis provoked by H. pylory, and in general in the presence of an inflammatory state affecting the gastrointestinal tract (IBD), the use of the known COX-2 inhibitors can facilitate the onset of ulcers (J. Clin. Gastroenterol. 2002 34, 451-453). Another drawback of these drugs is that the analgesic activity is not optimal.

The need was felt to have available drugs showing an improved COX-1/ COX-2 pharmacological performance, and being able to inhibit both the activity and expression of the enzyme COX-2 without presenting the aforesaid side-effects.

The Applicant has surprisingly and unexpectedly found drugs that are able to solve the aforementioned technical problem.

An object of the present invention is the use of compounds of formula (I) or salts thereof with an anti-inflammatory activity that are able to inhibit selectively the enzyme COX-2 without inhibiting substantially the enzyme COX-1, without showing side-effects, in particular at gastrointestinal, renal levels, and without damaging the cardiovascular apparatus:

$$R\text{-}T_1\text{-}B\text{-}C_{c0}\text{-}N(O)_s$$

(I)

wherein

$R\text{-}T_1\text{-}$ is a radical deriving from a non steroidal anti-inflammatory drug of formula $R\text{-}T_1OH$ or $R\text{-}T_1H$ wherein R is defined hereunder, T_1 is CO or X, wherein X is O, S, $N(R_{1C})$ wherein R_{1C} is H or a linear or branched $C_1\text{-}C_5$ alkyl;

c0 is an integer equal to 0 or 1;

s is an integer equal to 1 or 2, preferably 2;

B is a bivalent linker of formula (III)

$$-T_B\text{–}X_2\text{–}T_{B1}\text{-}$$

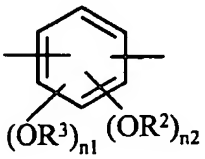
(III)

wherein

T_B and T_{BI} are equal or different and are CO or X wherein X is as defined above;

X_2 is a bivalent bridging group and is selected from the following compounds:

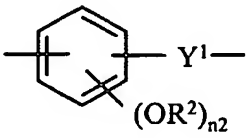
a)



wherein:

n1 and n2 are integers 0 or 1; $R^2$and R^3 are independently selected from H or CH_3;

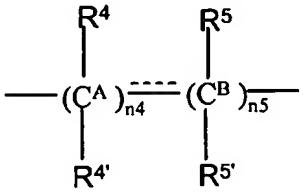
b)



wherein:

Y^1 is $-CH_2-CH_2-(CH_2)_{n2'}-$ or $-CH=CH-(CH_2)_{n2'}-$, wherein n2' is an integer from 0 to 10, and n2 and R^2 are as above defined;

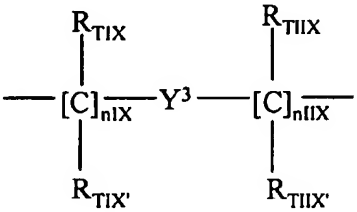
c)



wherein:

n4 is an integer from 1 to 20 and n5 is an integer from 0 to 20, R^4 and $R^{4'}$ R^5 and $R^{5'}$ are independently selected from H, CH_3, OH, NH_2, $NHCOCH_3$, COOH; when the bond between the C^A and C^B carbons is a double bond R^4 and R^5 or R4' and R^5 are absent;

d)



(III^p)

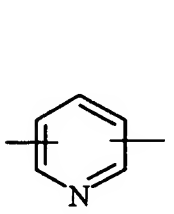
wherein:

nIX is an integer from 0 to 10, preferably from 1 to 5;

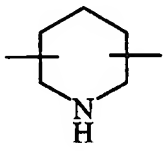
nIIX is an integer from 1 to 10, preferably from 1 to 5;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, are the same or different, and are H or straight or branched C_1-C_4-alkyl, preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H;

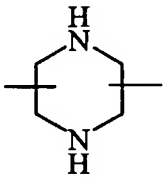
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring having 5 or 6 atoms, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, and selected from:



(Y1)



(Y2)



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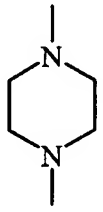

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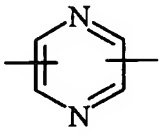

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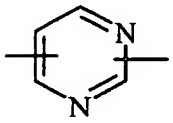

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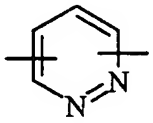
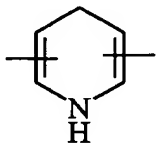
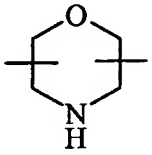


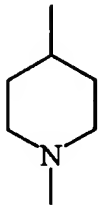
(Y7)



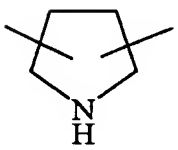
(Y8)



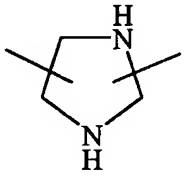
(Y9)



(Y10)



(Y11)



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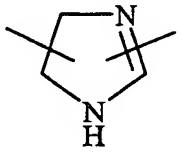
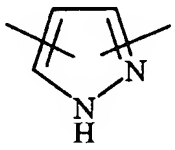
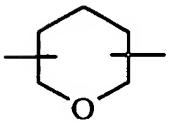


(Y13)



(Y14)



(Y15);

preferably Y^3 are: (Y1), having the two free valences in ortho position to the nitrogen atom, (Y4), (Y10);

C is the bivalent radical $-T_c-Y-$ wherein:

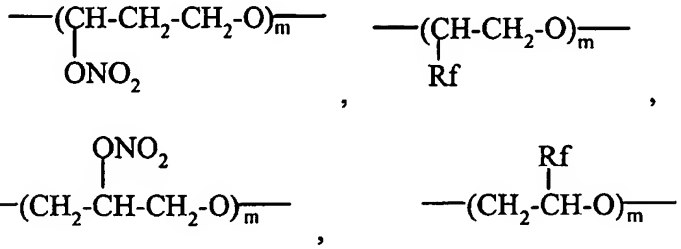
T_c is CO or X, wherein X is as above defined;

Y is a bivalent radical having the following meaning:

e)

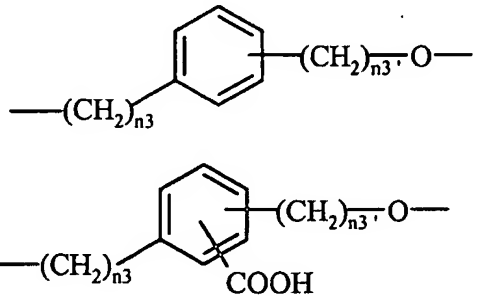
an alkylenoxy group -R' O- wherein R' is linear or when possible branched C_1 –C_{20}, alkylene preferably having from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylenic ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type wherein R' is as above defined;

f)



wherein m is an integer from 1 to 6, preferably from 1 to 4, R_{1f} is H or CH_3;

g)



wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;

with the proviso that:

when T_1 is CO then T_B is X wherein X is as defined above;

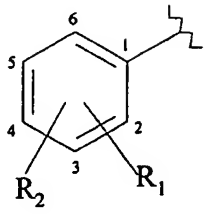
when T_1 is X wherein X is as defined above, then T_B is CO;

when c0 is 1, T_c is CO when T_{BI} is X wherein X is as above defined;

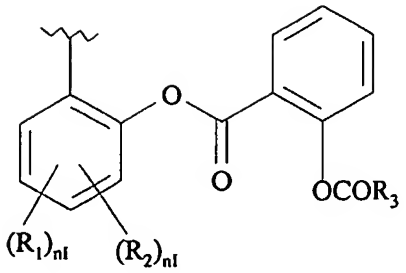
when c0 is 1, T_c is X wherein X is as above defined, when T_{BI} is CO;

when c0 is 0, T_{BI} has the only meaning of O;

the radical R, deriving from the non steroidal anti-inflammatory drugs of formula R-T_1OH, when T_1 is CO, or R-T_1H, when T_1 is X, is selected from:



(Ia)



(Ib)

in formula (Ia):

R_1 is H or -$OCOR_3$ wherein R_3 is methyl, ethyl or linear or branched C_3-C_5 alkyl,

R_2 is H, hydroxy, halogen atom, nitro, amino, mono- or di-(C_1-C_4) alkylamino, linear or when possible branched C_1-C_4 alkyl, linear or branched when possible C_1-C_4 alkoxy, a linear or when possible branched C_1-C_4 perfluoroalkyl, for example trifluoromethyl;

with the proviso that in formula (Ia) $R_1$and R_2 cannot contemporaneously be H, preferably when R_1 is H, R_2 is OH;

-when R_1 is -$OCOCH_3$ in position 2 and R_2 is hydrogen, Ia) represents the residue of acetylsalicylic acid;

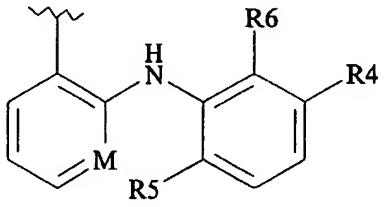
- when R_1 is H and R_2 is OH in position to 2, Ia) represents the residue of salicylic acid;

in formula (Ib):

nI is an integer equal to 0 or 1;

R_1, R_2 and R_3 are as defined above;

- when R_3 is CH_3, nI is 0, the compounds of formula Ib) is the residue of acetylsalicylsalicylic acid;



(Ic)

wherein in formula (Ic):

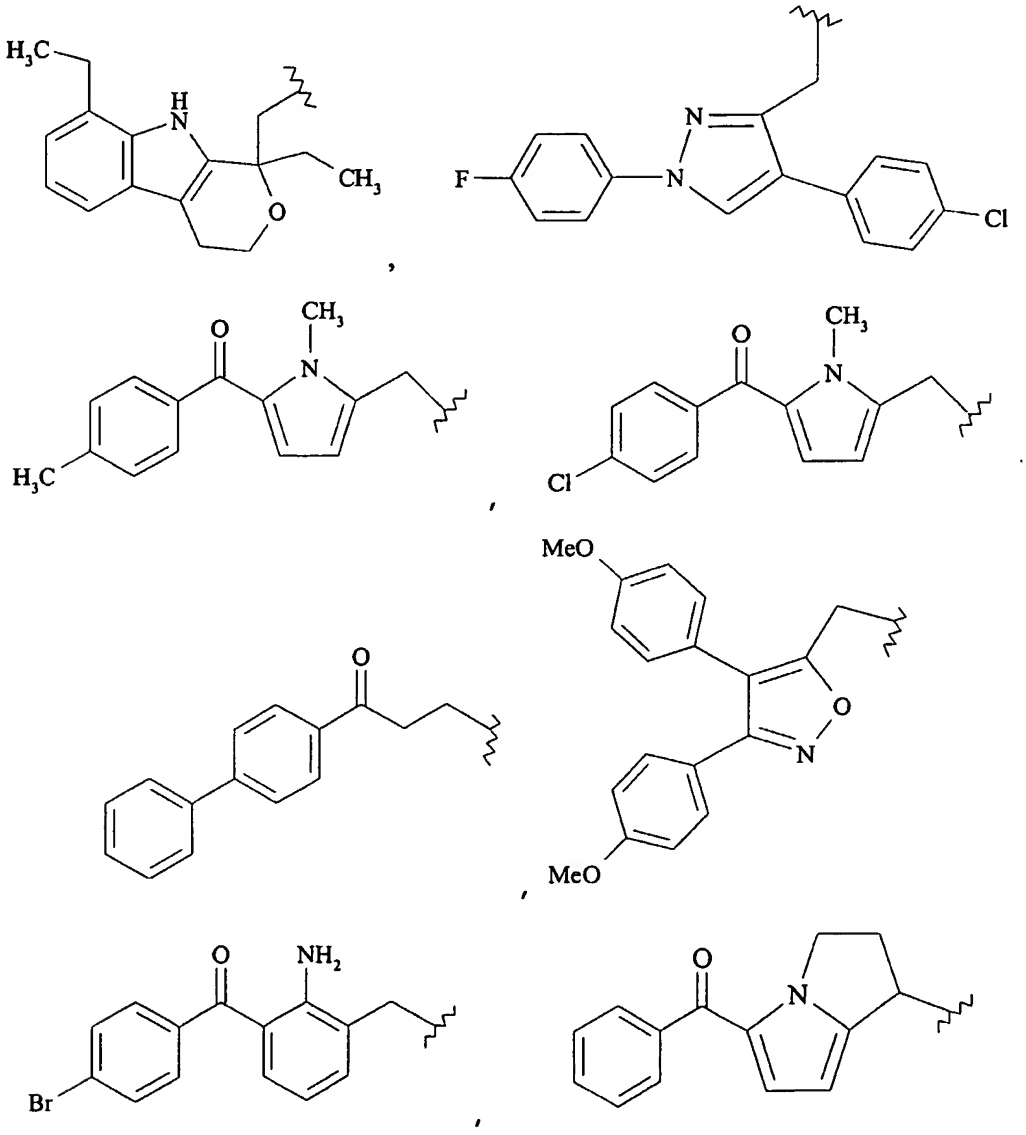
M is CH or N;

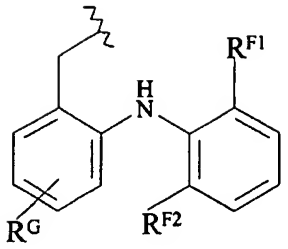
R6 is H, CH_3, an halogen atom preferably Cl,;

R4 is H, CF_3, CH_3 or an halogen atom preferably Cl,;

R5 is H, an halogen atom preferably Cl;

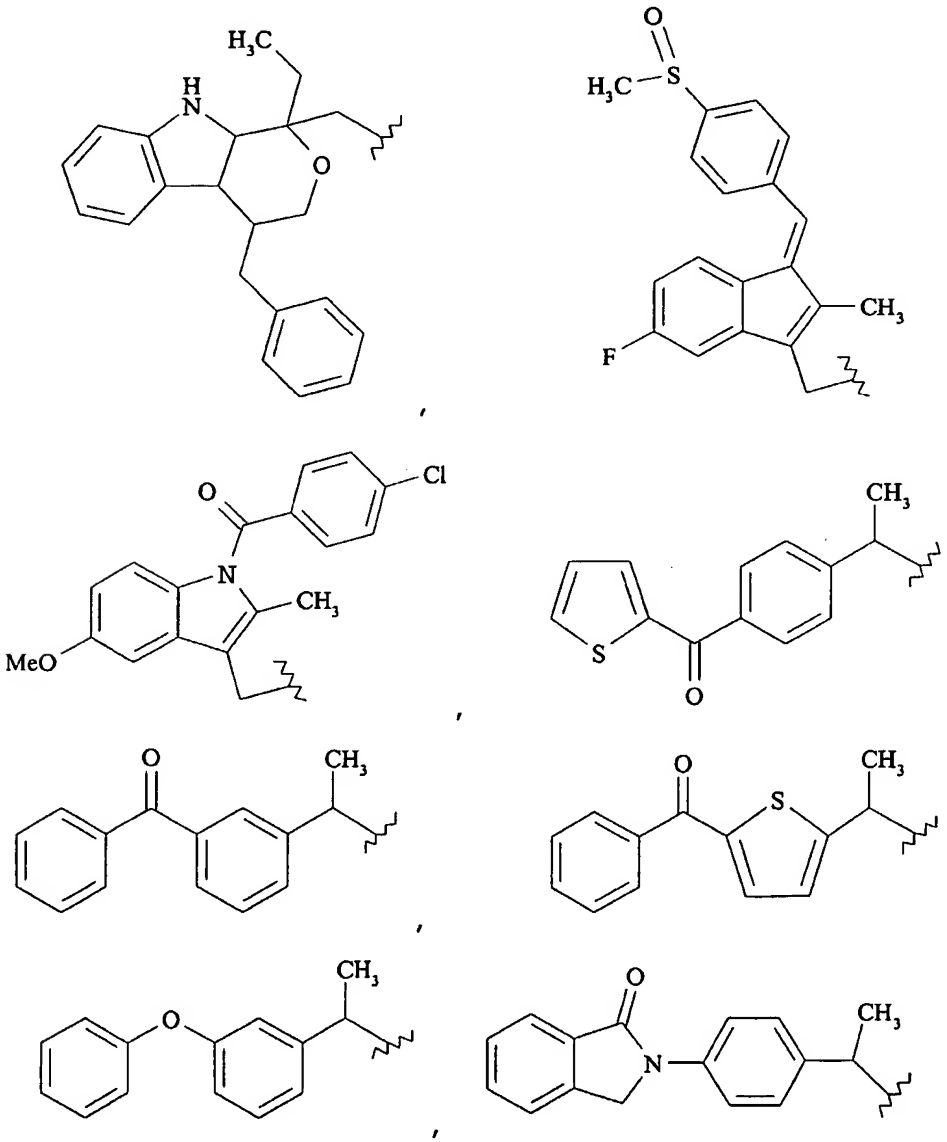
- when M is CH, R6 and R5 are H, R4 is CF_3, (Ic) is the residue of flufenamic acid;
- when M is CH, R6 and R5 are Cl, R4 is CH_3, (Ic) is the residue of meclofenamic acid;
- when M is CH, R6 and R4 are CH_3, R5 is H, (Ic) is the residue of mefenamic acid;
- when M is CH, R6 is CH_3, R5 is H, R4 is Cl, (Ic) is the residue of tolfenamic acid;
- when M is N, R6 and R5 are H, R4 is CF_3, (Ic) is the residue of niflumic acid;
- when M is N, R6 is CH_3, R5 is H, R4 is CF_3, (Ic) is the residue of flunixin;

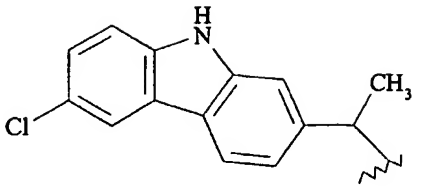
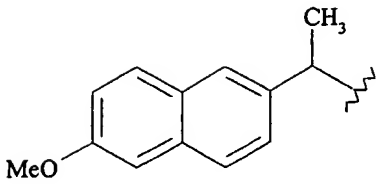
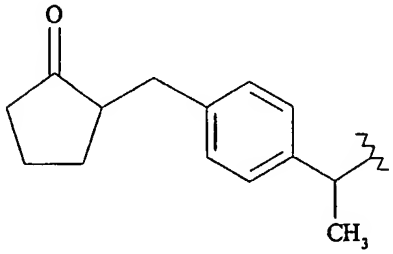
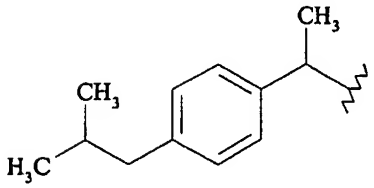
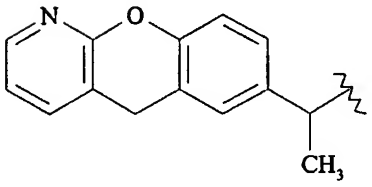
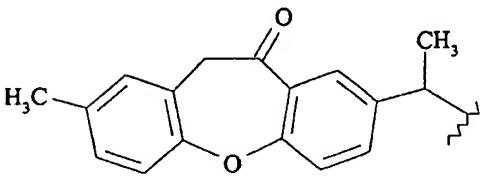
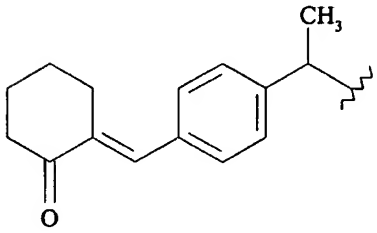
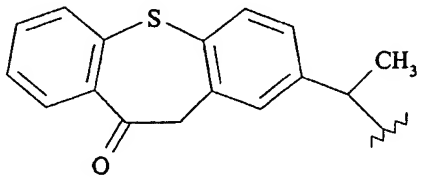
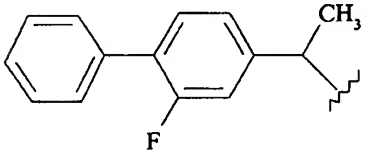
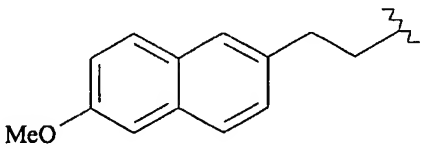
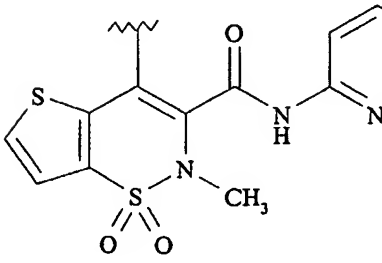
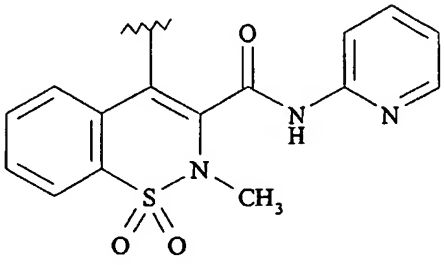


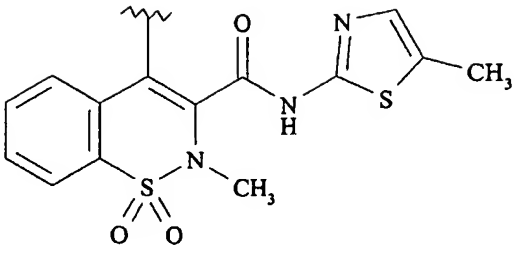


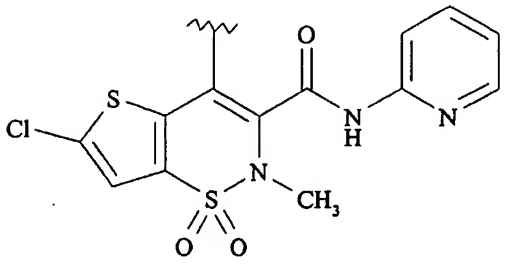
(IIa)

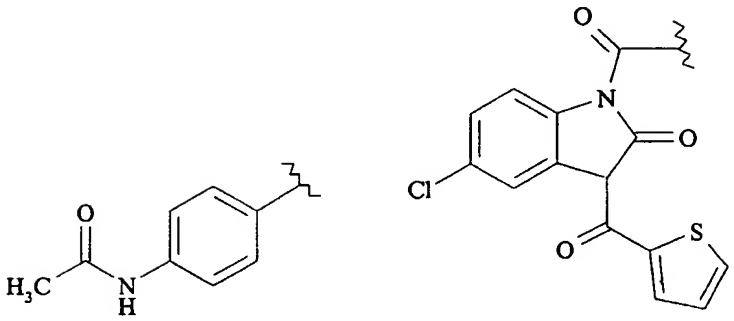
wherein R^{F1} and R^{F2} are independently selected from H or Cl, Br, F, R^G is hydrogen or , C_1-C_6 linear or branched alkyl, preferably R^G is methyl; when R^{F1} and R^{F2} are Cl and R^G is hydrogen the compound of formula (IIa) represents the residue of dichlophenac;









The NSAIDs of formulas R-T_1OH and R-T_1H, mentioned above, are commercially available compounds or can be prepared according to the known methods described in the prior art, for example, in "The Merck Index" 12a Ed. (1996), herein incorporated by reference. Example of anti-inflammatory compounds for use in the present inventions are: Aspirin, Salicylic acid, Mesalamine, Acetylsalicylsalicylic acid, 5-amino-acetylsalicylic acid, Flunixin, Ketorolac, Tolfenamic acid, Niflumic acid, Mefenamic acid, Meclofenamic acid, Flufenamic acid, Enfenamic acid, Etodolac, Pirazolac, Tolmetin, Bromefenac, Fenbufen, Mofezolac, Diclofenac, Pemedolac, Sulindac, Indomethacin, Suprofen, Ketoprofen, Tiaprofenic acid, Fenoprofen, Indoprofen, Carprofen, Naproxen, Loxoprofen, Ibuprofen, Pranoprofen, Bermoprofen, CS-670, Zaltoprofen, Flurbiprofen, Tenoxicam, Piroxicam, Meloxicam, Lornoxicam, Tenidap, Paracetamol and Salacetamide.

Example of precursor compounds of the bivalent radical B of formula (III), wherein the free valences of T_B and T_{BI} can be saturated with OH or H, for use in the present

invention are: penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, aspartic acid, gallic acid, ferulic acid, gentisic acid, citric acid, caffeic acid, dihydrocaffeic, p-coumaric acid, vanillic acid, dihydroxymaleic acid, glycolic acid, lactic acid, fumaric acid, 3-3'-thiodipropionic acid, p-coumaric alcohol, 4–hydroxyphenethylalcohol, conyferyl alcohol

Compounds of the present invention which have one or more asymmetric atoms can exist as the optically pure enantiomers, pure diastereoisomers, mixture of enantiomers, mixture of diastereoisomers, racemic mixtures of enantiomers, diasteroeisomeric racemates or mixtures of diastereoisomeric racemates. It is to be understood that the present invention anticipates and includes within its scope all such isomers or mixtures thereof.

Compounds of the inventions comprise a carbon-carbon double bond may exist as E or Z isomers, it is to be understood that the present invention anticipates and includes within its scope all such isomers or mixtures thereof.

The methods to prepare the compounds of formula (I) are described in patent applications WO 00/51988, WO 00/61537 and WO 00/61541, signed by the Applicant.

The compounds according to the present invention, when at least a functional group salifiable with acids is present, for example an amino group, can be transformed into the corresponding salts. For example a method to form salts is the following: when in the molecule one basic nitrogen atom is present, it is reacted in organic solvent as, for instance, acetonitrile, tetrahydrofuran, with an equimolecular amount of the corresponding organic or inorganic acid. Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric, trifluoroacetic acids. Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids.

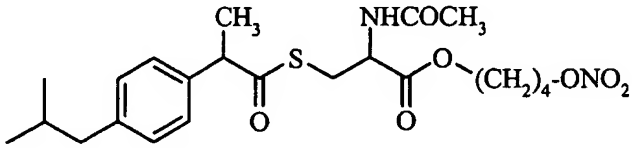
The compounds object of the present invention are formulated in the corresponding pharmaceutical compositions, even at delayed release, for parental, oral and topic use, as for example inhalatory, suppository, transdermal, enema use, according to the well known methods in the art, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences", 15a Ed.

The amount on molar basis of the active principle in these formulations is generally the same, or lower, in comparison with that of the corresponding precursor drug.

The daily administrable doses are those of the precursor drugs, or in the case lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk Reference".

Among the compounds of the invention the following ones are preferred:

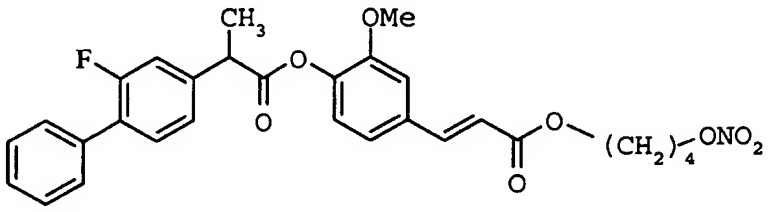
(S)-N-acetyl-[α-methyl-4-(2-methylpropyl)benzeneacetyl] ysteine 4 -nitrooxybutyl ester having formula:



;

(IV^C)

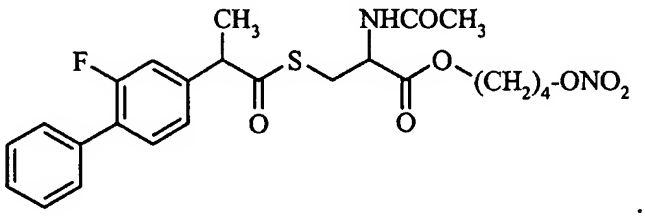
trans–3–[4–[2–fluoro–α–methyl(1,1'–biphenyl)–4–acetyloxy]–3–methoxyphenyl]–2–propenoic acid 4–(nitrooxy)butyl ester, having formula:



;

(VI^C)

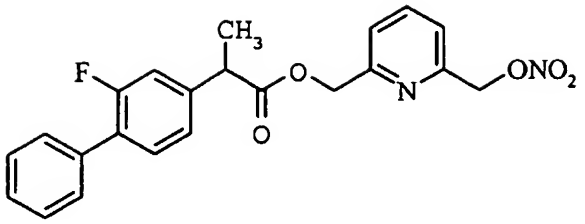
(S)–N–acetyl–[2–fluoro–α–methyl(1,1'–biphenyl)–4–acetyl]cysteine 4–(nitrooxy)butyl ester having formula:



;

($VIII^C$)

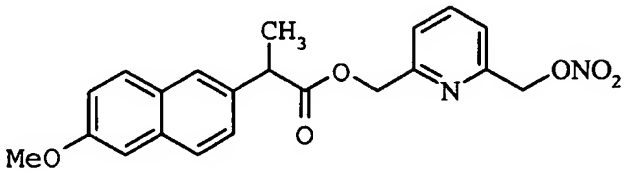
2–fluoro–α–methyl[1,1'–biphenyl]–4–acetic acid 6–(nitrooxymethyl)–2–methylpyridyl ester having formula:



;

(XI^C)

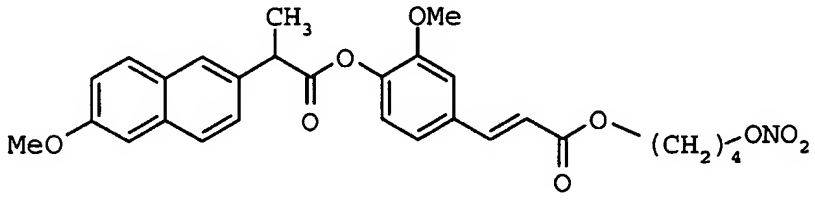
(S)–6–methoxy–α–methyl–2–naphtaleneacetic acid 6–(nitrooxymethyl)–2–methylpyridyl ester having formula:



;

(XII^C)

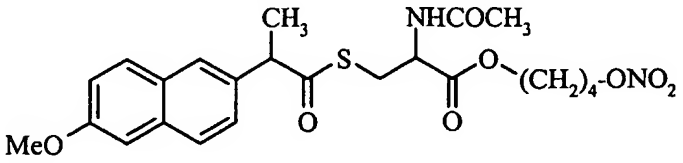
trans–3–[4–[6–methoxy–α–methyl–2–naphtaleneacetyloxy]–3–methoxyphenyl]–2–propenoic acid 4 – (nitrooxy)butyl ester having formula:



;

(XIII^C)

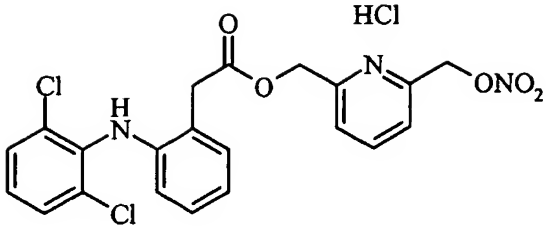
(S,S)–N–acetyl–S–(6–methoxy–α–methyl–2–naphtaleneacetyl)cysteine 4–(nitrooxy)butyl ester having formula:



;

(XIV^C)

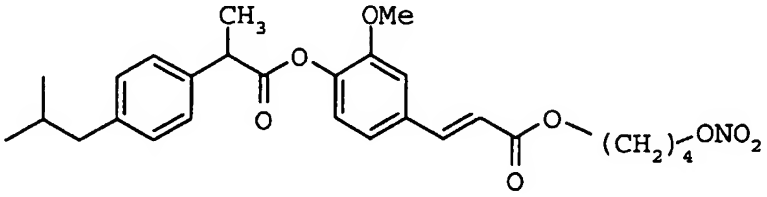
2–[(2,6–dichlorophenyl)amino]benzene acetic acid 6–(nitrooxymethyl)–2–methylpyridyl ester hydrochloride having formula:



;

(XVI^C)

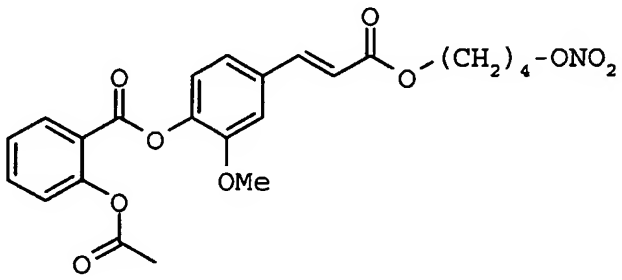
trans–3–[4–α–methyl–4–(2–methylpropyl)benzoyl acetate]–3–methoxyphenyl]-2–propenoic acid 4–(nitrooxybutyl) ester having formula:



;

(XVII^C)

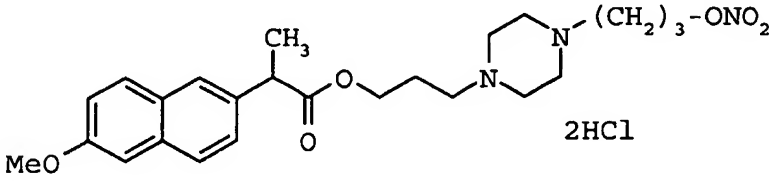
trans–3–[4–acetylbenzoyloxy]–3–methoxyphenyl]-2–propenoic acid 4–(nitrooxybutyl) ester having formula:



;

(XVIII^C)

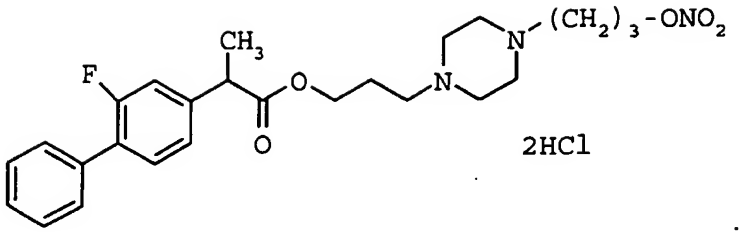
(S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride having formula:



;

(XIX^C)

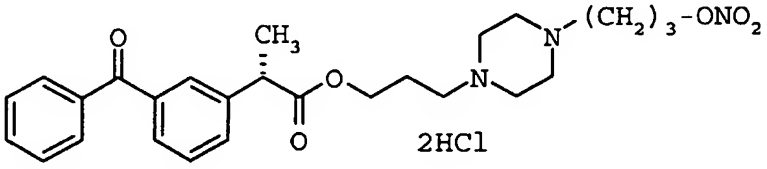
2–fluoro–α–methyl–[1,1'–biphenyl]–4–acetic acid-3-[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride having formula:



;

(XX^C)

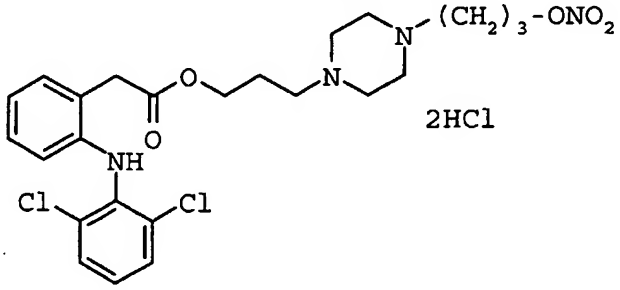
(S)–3–enzoyl–α–methyl–benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride having formula



;

(XXI^C)

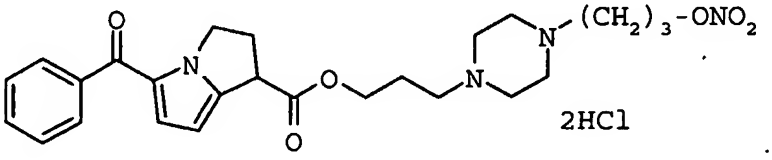
2–[(2,6–dichlorophenyl)amino]benzeneacetic acid–3-[4–(3–nitrooxypropyl)–1–piperzinyl]propyl ester dihydrochloride having formula:



;

($XXII^C$)

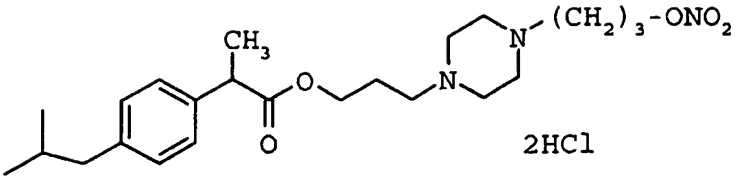
5–benzoyl–2,3–dihydro–3H–pyrrole[1,2–a]pyrrole–1–carboxylic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride having formula:



;

($XXIII^C$)

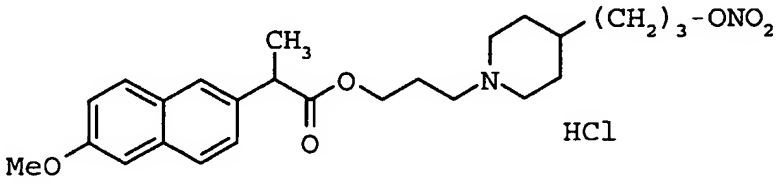
α–methyl–4–(2–methyl–propyl)benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride having formula:



;

(XXIV^C)

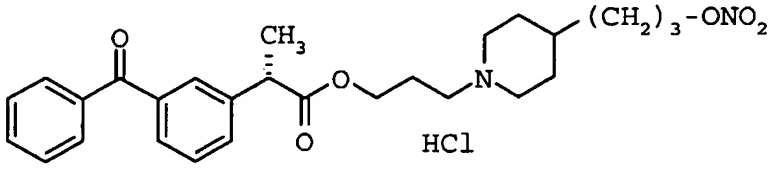
(S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–nitroxypropyl)–1–piperidinyl]propyl ester hydrochloride having formula:



;

(XXV^C)

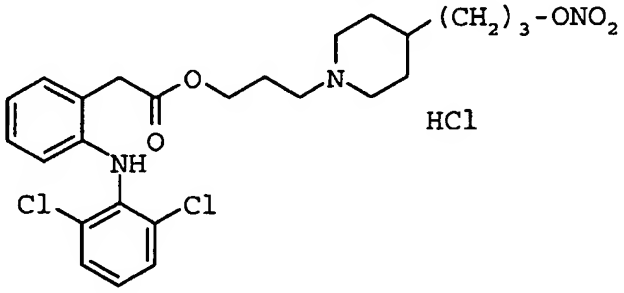
(S)–3-benzoyl–α–methyl–benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperidinyl]propyl ester hydrochloride having formula:



;

(XXVI^C)

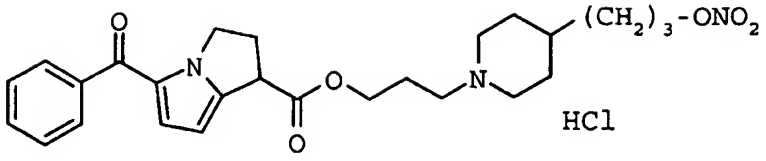
2–[(2,6–dichlorophenyl)amino]benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperidinyl]propyl ester hydrochloride having formula:



;

(XXVII^C)

5–benzoyl–2,3–dihydro–3H–pyrrole[1,2–a]pyrrole–1-carboxylic acid–3–[4–(3–nitrooxypropyl)–1–piperidinyl]propyl ester hydrochloride having formula:



(XXVIII^C)

Surprisingly, the compounds of the invention can inhibit substantially selectively COX-2 without showing a marked inhibitory effect on COX-1. These results are even more surprising if it is considered the fact that the precursors are not selective COX-2 inhibitors. Moreover, even the same compounds of the invention but without the presence of the bivalent linker –B-of formula (III) have resulted non- selective towards the COX-2. See the comparative examples.

Furthermore, the compounds of the present invention do not present any side-effect at gastric, cardiovascular and renal levels, and at the same time they also show a good analgesic activity.

The compounds of the present invention can be used for the treatment of diseases having an inflammatory origin, osteoarthritis, rheumatoid arthritis, dysmenorrhea, pain, fever, and for the treatment and / or the prevention of troubles caused by high levels of COX-2.

The following examples have an illustrative purpose for the invention, and not a limitative one.

EXAMPLES

EXAMPLE 1

Synthesis of (S)-6-methoxy-α- methyl-2-naphtaleneacetic acid, 3-[4-(3-nitrooxypropyl)-1-piperazinyl]-propyl ester dihydrochloride (XIX^c)

A) Synthesis of (S)-6-methoxy-α-methyl-2-naphtaleneacetic acid, 3-bromopropyl ester

To a solution of 1,3-dibromopropane (2.42 ml) in DMF (50 ml) a suspension of naproxen sodium salt (2g, 7.93 mmoles) in DMF (50 ml) was added in small portions and the suspension was kept under stirring at room temperature for 24 hours. Then, water (200 ml) was added to the suspension, and the organic phase was extracted by ethyl ether (100 ml x 3). The reunited organic phases were anydrified and the solvent was evaporated at reduced pressure. The crude product of reaction was purified by

chromatography on silica gel eluting with hexan /ethyl acetate (9/1 v/v) to give 2.15g of (S)-6-methoxy-α-methyl-2-naphtaleneacetic-3-bromopropyl ester.

B) Synthesis of (S)-6-methoxy-α-methyl-2-naphtaleneacetic acid-3-[4-(3-chloropropyl)-1-piperazinyl]propyl ester

To a solution of (S)-6-methoxy-α-methyl-2-naphtaleneacetic acid-3-bromopropyl ester (1.5 g, 4.3 mmoles) in THF (20 ml) at 40 °C, a solution of N–(3–chloropropyl)piperazine dihydrochloride (1g, 4.3 mmoles), synthesized as described in the example 1A hereinafter reported, in THF (25 ml), DMF (20 ml) and triethylamine (TEA) (2 ml) was added. The resulting solution was heated at 55 °C for 24 hours. Then the solution was cooled and extracted by ethyl ether; the reunited organic phases were washed with water, dried over Na_2SO_4 and filtered. The solvent was evaporated at reduced pressure and the residue was purified by chromatography on silica gel eluting with ethyl acetate /TEA (10/0.4 v/v) to give 0.725 g of (S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–chloropropyl)–1–piperazinyl]propyl ester.

^{1}H NMR ($CDCl_3$): 7.67 (3H, m); 7.39 (1H, dd); 7.11 (2H, m); 4.11 (2H, m); 3.9 (3H, s); 3.85 (1H, q); 3.56 (2H, t); 2.42-2.21 (12H, m); 1.90 (2H, m); 1.70 (2H, m); 1.56 (3H, d).

C) Synthesis of (S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester

To a solution of (S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3-[4-(3–chloropropyl)–1–piperazinyl]propyl ester (0.7 g, 1.6 mmoles) in acetonitrile (50 ml) $AgNO_3$ (0.545 g, 3.2 mmoles) was added and the solution was heated at 60 °C kept away from light for 24 hours. Salts were filtered, the solvent was evaporated, and the obtained crude product was purified by chromatography on silica gel eluting with ethyl acetate/ TEA (10/0.4 v/v) to give (S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–nitroxypropyl)–1–piperazinyl]propyl ester (0.1 g).

^{1}H NMR ($CDCl_3$): 7.67 (3H, m); 7.39 (1H, dd); 7.11 (2H, m); 4.5 (2H, t); 4.11 (2H, m); 3.9 (3H, s); 3.85 (1H, q); 3.56 (2H, t); 2.42- 2.21 (12H, m); 1.90 (2H, m); 1.70 (2H, m); 1.56 (3H, d).

D) Synthesis of (S)-6–methoxy–α–methyl–2–naphthalenacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride

To a solution of (S)–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–nitroxypropyl)–1–piperazinyl]propyl ester (0.1 g, 0.22 mmoles) in ethyl acetate cooled

in an ice bath, HCl/ethyl acetate (0.2 ml, 2.5 N) was dripped, after 1 hour the temperature of the suspension was left to return to room temperature. The solid product was filtered, washed with ethyl ether and dried up at reduced pressure.

EXAMPLE 1A

Synthesis of N–(3–chloropropyl)–piperazine dihydrochloride

To a solution of N–Boc–piperazine (2 g) in CH_2Cl_2 (40 ml) and TEA (1.8 ml), cooled at 0 °C, 3–chloro–1–bromopropane (1.3 ml) was added and the solution was heated at 50 °C for 3 hours. The solvent was evaporated at reduced pressure and the residue was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried over Na_2SO_4 and filtered, the solvent evaporated at reduced pressure and the crude product was purified by chromatography on silica gel eluting with ethyl acetate/hexane (8/2 v/v) to obtain N'–(3–chloropropyl)–N–Boc–piperazine (1.7 g).

N'–(3–chloropropyl)–N–Boc–piperazine was dissolved in HCl/ethyl acetate(10 ml), the solution was cooled at 0 °C in an ice bath and stirred for 1 hour at 0 °C then it is left to return to room temperature. The solvent was eliminated and the residue was treated with diethyl ether and the obtained solid product was filtered and used without any further purification..

EXAMPLE F1

In vitro determination of COX-2 activity by WHMA (William Harvey Human-modified whole blood Assay) and of COX-1 activity by WBA (Whole Blood Assay)

DETERMINATION OF COX-2 ACTIVITY

Human bronchial epithelial A459 cells set in 96-well plates in the presence of the culture medium DMEM (Dulbecco's modified eagle's medium), additivated with fetal bovine serum (10%) and L-glutamine (2 mM), were treated with interleukin -1β for 24 hour in order to induce the expression of COX-2.

After 24 hours human blood (100 microlitres) and solutions (DMSO 0.1% v/v) of the compounds to be tested at 5 different concentrations, from 10^{-3} M to 10^{-9} M were added to the cells, and the control plates were treated with the carrier.

60 minutes after the adding of the compounds, the plates were treated with calcium ionophore A23187 (50 μM) and after 30 minutes with dichlophenac to inhibit the

enzyme COX-1 (1 mM). 15 minutes after, the cells were centrifuged and the plasma removed. The COX-2 activity of the tested compounds was determined as concentration of PGE2 present in the samples, determined by a radioimmunologic method (Amersham, Oakville, Ontario Canada). Results are reported in Table I and are expressed as the dose inhibiting 50% of COX activity (IC_{50}).

DETERMINATION OF COX-1 ACTIVITY

Aliquots (100-µl) of venous human blood treated with heparin (19 U/ ml) were transferred on a 96-well plates and treated with solutions (DMSO 0.1% v/v) of the tested compounds of concentrations from 10^{-3} M and 10^{-9} M. The control plates have been treated with the solvent (DMSO 0.1% v/v).

60 minutes after the adding of the compounds the plates were treated with calcium ionophore A23187 (50 µM) and 30 minutes after, the plates were centrifuged (1500 Rpm, 4 °C, 5 minutes), the plasma removed and immediately frozen.

The COX-1 activity of the samples was determined as concentration of TXB2 by radioimmunologic method (Amersham, Oakville, Ontario Canada). Results, expressed as IC_{50}s are reported, are reported in Table I.

The compounds used are the following:

- Ibuprofen;
- (S)–N–acetyl–S–α–methyl-[4–(2–methylpropylbenzene]acetyl)cysteine 4–nitrooxybutyl ester (NO–cys–ibuprofen), synthesized as described in WO 00/61537, example 2;
- flurbiprofen;
- trans–3–[4–[2–fluoro–α–methyl–(1,1')–biphenyl–4–acetyloxy]-3–methoxyphenyl]–2–propenoyl–4–nitrooxy)butyl ester (NO–fer–flurbiprofen), synthesized as described in WO 00/61537, example 6;
- flurbiprofen 4–nitroxybutyl ester (NO–flurbiprofen), synthesized as described in WO 95/ 30641.

EXAMPLE F2

Evaluation of analgesic activity

The experiments were conducted as described by Moore et al., J. Pharmacol. 1991, 102, 198-202.

Rats weighing 20 g, were treated i.p. with acetic acid (2% w/v in saline solution pH 2.7, 10 ml /kg) and after 15 minutes the animals were treated p.o. with the tested compounds at doses as indicated in Table 2 or with the carrier (carboxymethylcellulose 0.5 % w/ v; 10 ml/ kg) and immediately set in single cages where the number of abdominal contractions were calculated for 30 minutes. The results reported in Table are expressed as inhibition percentage of the abdominal contractions induced by acetic acid in comparison with non-treated controls.

EXAMPLE F3

Evaluation of gastric and vascular damage

The experiments were carried out as described in M.N. Muscarà et al., Br. J. Pharmacol. 133, 1314, 2001.

Rats weighing 200-250g, divided in groups of 10 animals each, were treated p.o. with the tested compounds indicated in F1 (suspended in carboxymethylcellulose 1%) at the daily doses reported in Table 3, for two weeks.

In these rats arterial hypertension was induced by adding L-NAME (N-omega-nitro-L-arginine methyl ester) in drinking water, at a concentration of 400 mg/l.

Sixteen hours after the last administration, hematic pressure was determined by cannulating femoral artery, and measured by polygraphic transductor. Later, rats were sacrificed and the gastric damage was noticed, determining the percentage of animals that presented gastric damage.

The results reported in Table 3 show that the products of the invention are well tolerated at gastric level, while celecoxib, the COX-2 inhibitor taken as reference drug, and the precursor drugs provoke gastric damage on a percentage between 80 and 100% in the animals.

Celecoxib and precursor drugs cause an elevation of pressure, while the drugs of the present invention do not influence the cardiovascular parameters.

Table 1

Evaluation of COX-1 and COX-2 activities of the compounds of the present invention, in comparison with Celecoxib, a COX-2 inhibitor, with the precursor anti-inflammatory compounds and with the corresponding nitroxyderivatives according to WO 95/30641.

Compound	*COX-1 IC_{50} (M)*	*COX-2 IC_{50} (M)*	*COX-1/COX-2 Ratio IC_{50}*
Celecoxib (cf.)	1.2	0.34	3.3
Ibuprofen (cf.)	$7.6\ 10^{-6}$	$1.95\ 10^{-5}$	0.4
NO–cys–ibuprofen	$9.23\ 10^{-5}$	$7.7\ 10^{-8}$	1198.7
Flurbiprofen (cf.)	$7.54\ 10^{-8}$	$1.14\ 10^{-6}$	0.07
NO–fer-flurbiprofen	$1.06\ 10^{-5}$	$3.6\ 10^{-8}$	294.4
NO–flurbiprofen (cf.)	$5.25\ 10^{-7}$	$5\ 10^{-7}$	1.05

Table 2

Evaluation of the analgesic activity of the compounds of the present invention in comparison with the precursor anti-inflammatory drugs and with the correspondent nitroxyderivatives according to WO 95/30641

Compound	*Dose (mg/kg)*	*% of inhibition of abdominal contractions Vs. controls*
Celecoxib (cf.)	10	0
Ibuprofen (cf.)	30	32
NO-cys–ibuprofen	60	85
Flurbiprofen (cf.)	3	25
NO–fer–flurbiprofen	20	72
NO–flurbiprofen (cf.)	20	63

Table 3

Determination of gastric damage and of cardiovascular parameters of the compounds of the present invention, in comparison with Celecoxib, with the precursor anti-inflammatory compounds and with the correspondent nitroxyderivatives according to WO 95/ 30641

Compound	*Dose (mg/ kg)*	*% animals with gastric damage*	*Arterial pressare (mmHg)*
Carrier	-	50	140
Celecoxib (cf.)	10	80	170
Ibuprofen (cf.)	30	100	160
NO–cys–ibuprofen	60	0	138
Flurbiprofen (cf.)	3	100	167
NO–fer–flurbiprofen	20	0	135
NO–flurbiprofen (cf.)	20	30	150

CLAIMS

1. Use of compounds of formula (I) or salts thereof for the preparation of COX-2 inhibitor drugs:

$$R\text{-}T_1\text{-}B\text{-}C_{c0}\text{-}N(O)_s$$

(I)

wherein

$R\text{-}T_1$- is a radical deriving from a non steroidal anti-inflammatory drug of formula $R\text{-}T_1OH$ or $R\text{-}T_1H$ wherein R is defined hereunder, T_1 is CO or X, wherein X is O, S, $N(R_{1C})$ wherein R_{1C} is H or a linear or branched C_1-C_5 alkyl;

c0 is an integer equal to 0 or 1;

s is an integer equal to 1 or 2;

B is a bivalent linker of formula (III)

$$-T_B\text{–}X_2\text{–}T_{BI}\text{-}$$

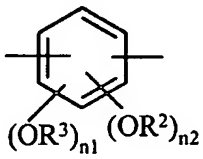
(III)

wherein

T_B and T_{BI} are equal or different and are CO or X wherein X is as defined above;

X_2 is a bivalent bridging group and is selected from the following compounds:

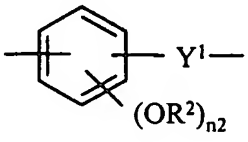
a)



wherein:

n1 and n2 are integers 0 or 1; $R^2$and R^3 are independently selected from H or CH_3;

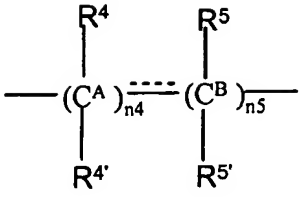
b)



wherein:

Y^1 is $–CH_2\text{-}CH_2\text{-}(CH_2)_{n2'}$- or $–CH{=}CH\text{-}(CH_2)_{n2'}$-, wherein n2' is an integer from 0 to 10, and n2 and R^2 are as above defined;

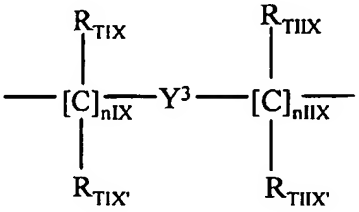
c)



wherein:

n4 is an integer from 1 to 20 and n5 is an integer from 0 to 20, R^4 and $R^{4'}$ R^5 and $R^{5'}$ are independently selected from H, CH_3, OH, NH_2, $NHCOCH_3$, COOH; when the bond between the C^A and C^B carbons is a double bond R^4 and R^5 or R4' and R^5 are absent;

d)



(III^p)

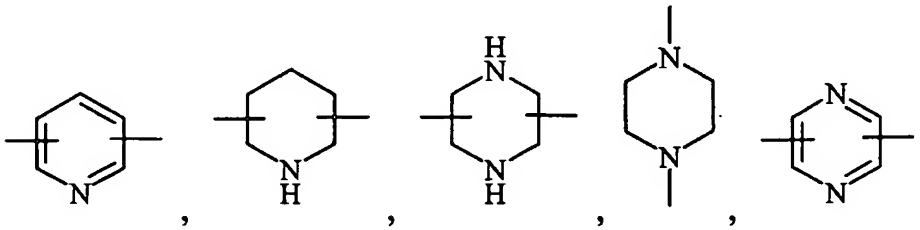
wherein:

nIX is an integer from 0 to 10;

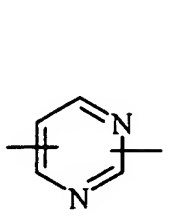
nIIX is an integer from 1 to 10;

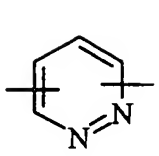
R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, are the same or different, and are H or straight or branched C_1-C_4-alkyl;

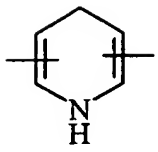
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring having 5 or 6 atoms, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, and selected from:

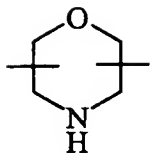


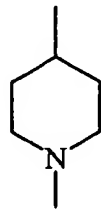
(Y1) (Y2) (Y3) (Y4) (Y5)

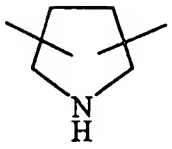

(Y6)

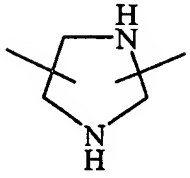

(Y7)

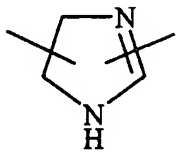

(Y8)

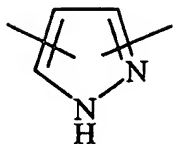

(Y9)

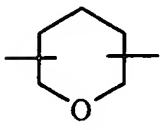

(Y10)


(Y11)


(Y12)


(Y13)


(Y14)


(Y15);

C is the bivalent radical $-T_c-Y-$ wherein:

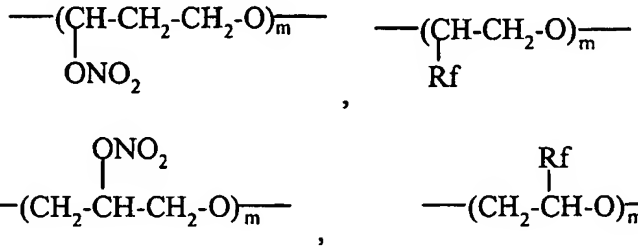
T_c is CO or X, wherein X is as above defined;

Y is a bivalent radical having the following meaning:

e)

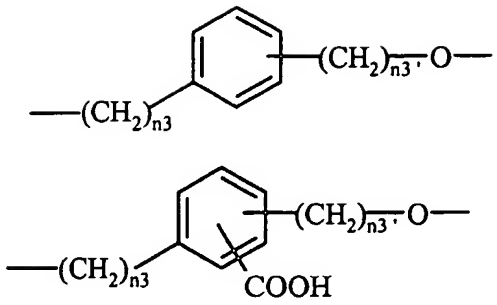
an alkylenoxy group -R' O- wherein R' is linear or when possible branched C_1 –C_{20}, alkylene preferably having from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylenic ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type wherein R' is as above defined;

f)



wherein m is an integer from 1 to 6, R_{1f} is H or CH_3;

g)



wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;

with the proviso that:

when T_1 is CO then T_B is X wherein X is as defined above;

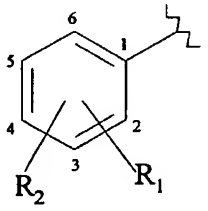
when T_1 is X wherein X is as defined above, then T_B is CO;

when c0 is 1, T_c is CO when T_{BI} is X wherein X is as above defined;

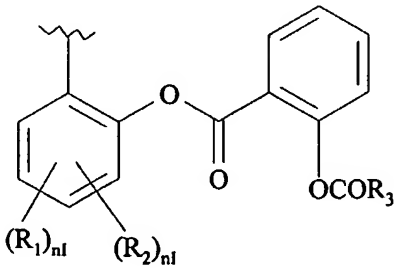
when c0 is 1, T_c is X wherein X is as above defined, when T_{BI} is CO;

when c0 is 0, T_{BI} has the only meaning of O;

the radical R, deriving from the non steroidal anti-inflammatory drugs o f formula R-T_1OH or R-T_1H, is selected from:



(Ia)



(Ib)

in formula (Ia):

R_1 is H or -$OCOR_3$ wherein R_3 is methyl, ethyl or linear or branched C_3-C_5 alkyl,

R_2 is H, hydroxy, halogen atom, nitro, amino, mono- or di-(C_1-C_4) alkylamino, linear or when possible branched C_1-C_4 alkyl, linear or branched when possible C_1-C_4 alkoxy, a linear or when possible branched C_1-C_4 perfluoroalkyl, for example trifluoromethyl;

with the proviso that in formula (Ia) $R_1$and R_2 cannot contemporaneously be H;

-when R_1 is –$OCOCH_3$ in position 2 and R_2 is hydrogen, Ia) represents the residue of acetylsalicylic acid;

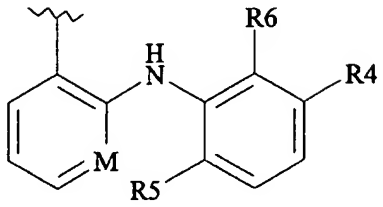
- when R_1 is H and R_2 is OH in position to 2, Ia) represents the residue of salicylic acid;

in formula (Ib):

nI is an integer and is equal to 0 or 1;

R_1, R_2 and R_3 are as defined above;

- when R_3 is CH_3, nI is 0, the compounds of formula Ib) is the residue of acetylsalicylsalicylic acid;



(Ic)

wherein in formula (Ic):

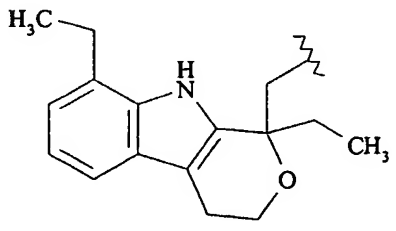
M is CH or N;

R6 is H, CH_3, an halogen atom preferably Cl,;

R4 is H, CF_3, CH_3 or an halogen atom preferably Cl,;

R5 is H, an halogen atom preferably Cl;

- when M is CH, R6 and R5 are H, R4 is CF_3, (Ic) is the residue of flufenamic acid;
- when M is CH, R6 and R5 are Cl, R4 is CH_3, (Ic) is the residue of meclofenamic acid;
- when M is CH, R6 and R4 are CH_3, R5 is H, (Ic) is the residue of mefenamic acid;
- when M is CH, R6 is CH_3, R5 is H, R4 is Cl, (Ic) is the residue of tolfenamic acid;
- when M is N, R6 and R5 are H, R4 is CF_3, (Ic) is the residue of niflumic acid;
- when M is N, R6 is CH_3, R5 is H, R4 is CF_3, (Ic) is the residue of flunixin;



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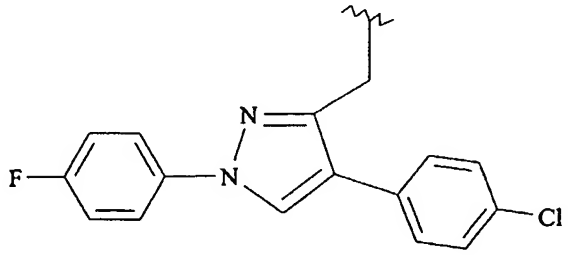

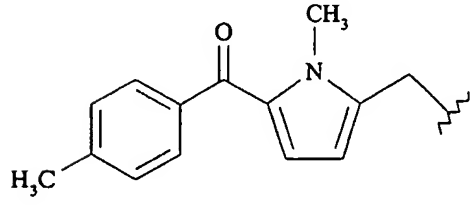

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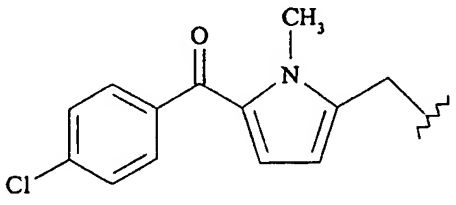
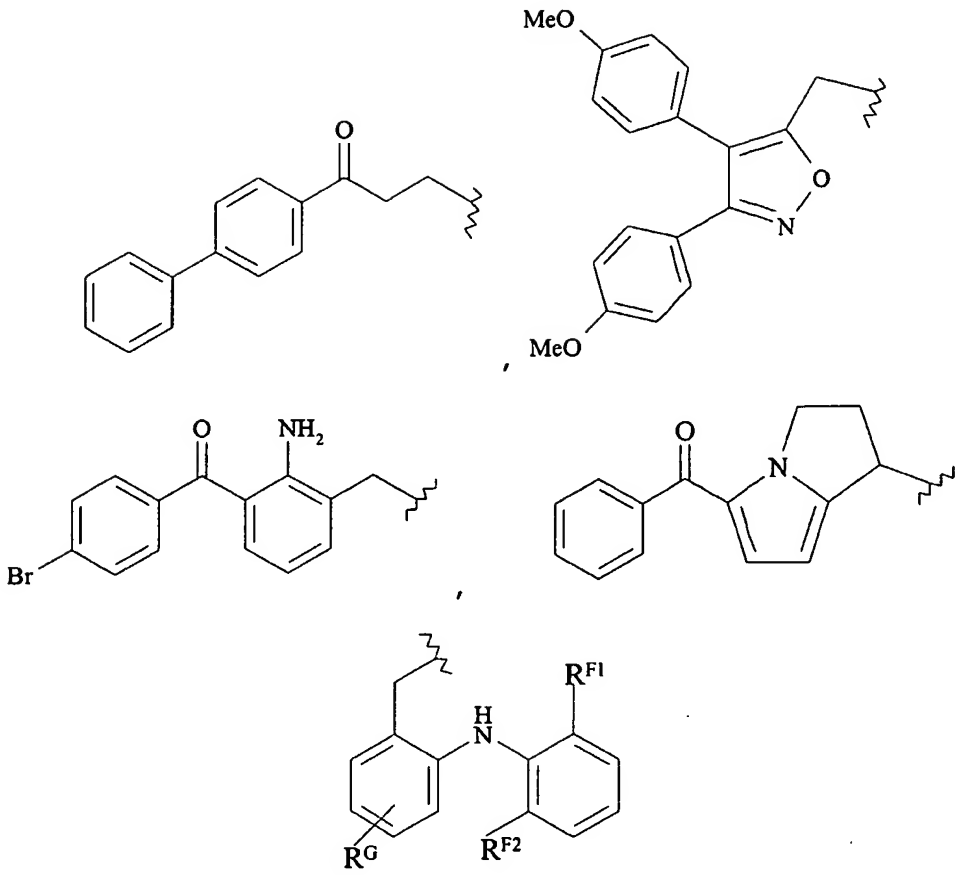
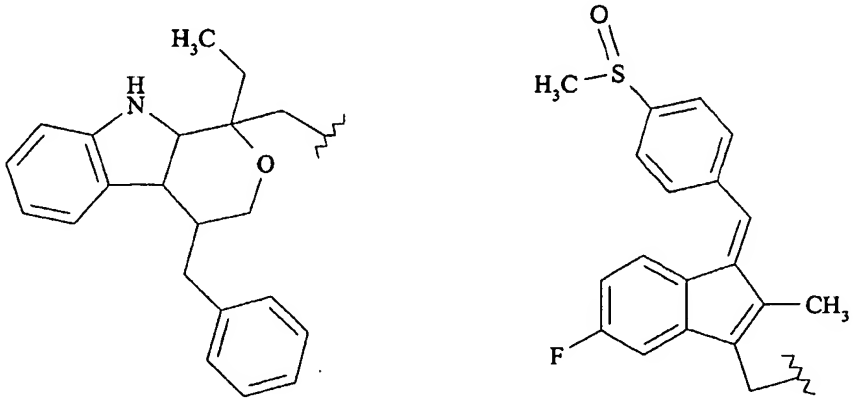


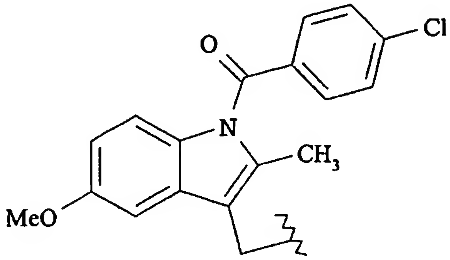
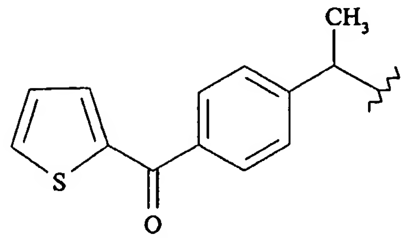


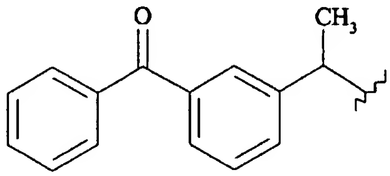
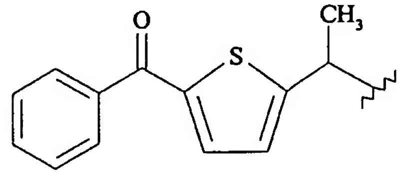
(IIa)

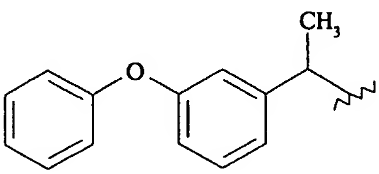
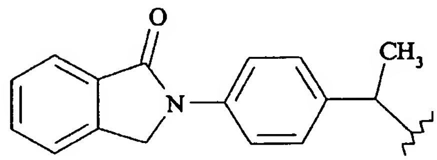
wherein R^{F1} and R^{F2} are independently selected from H or Cl, Br, F, R^G is hydrogen or, C_1-C_6 linear or branched alkyl;

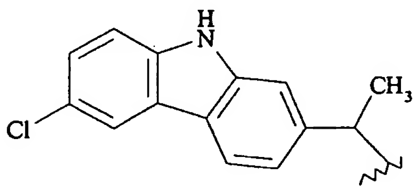
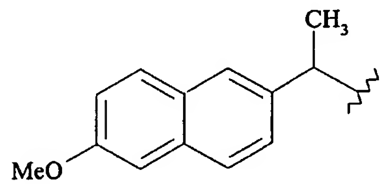
- when R^{F1} and R^{F2} are Cl and R^G is hydrogen the compound of formula (IIa) represents the residue of dichlophenac;

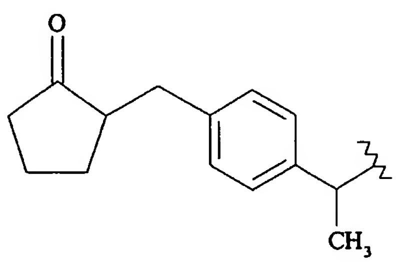
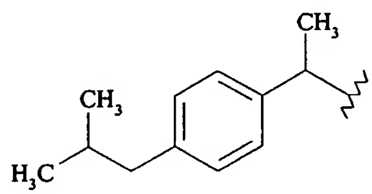


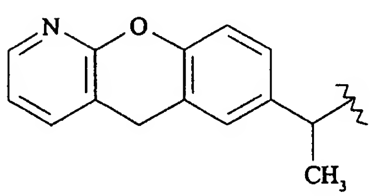
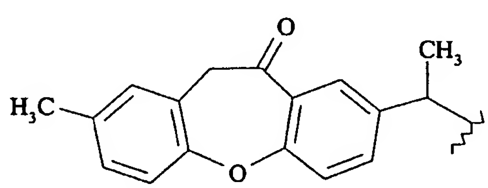
  ,

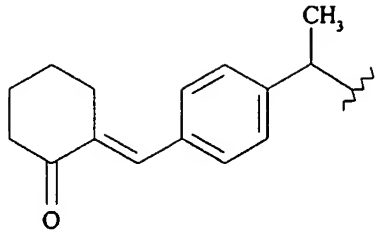
  ,

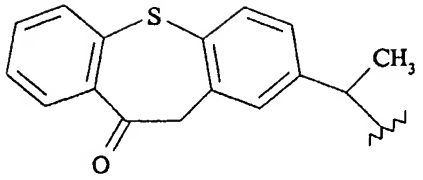
  ,

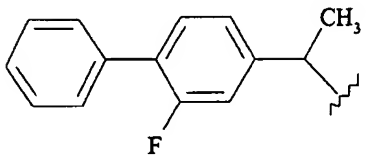
 , 

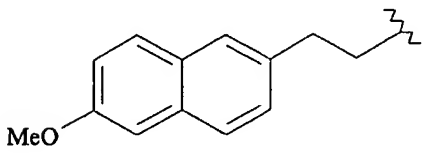
 , 

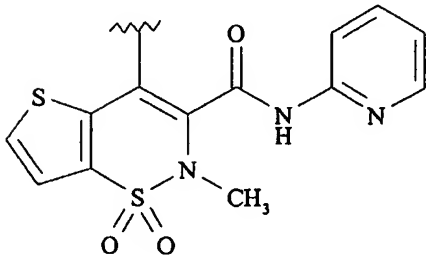
 , 

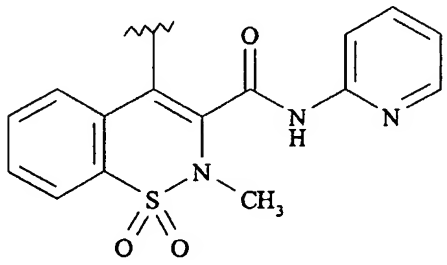


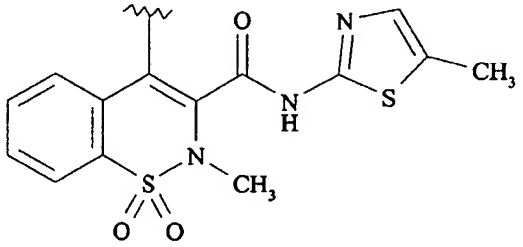


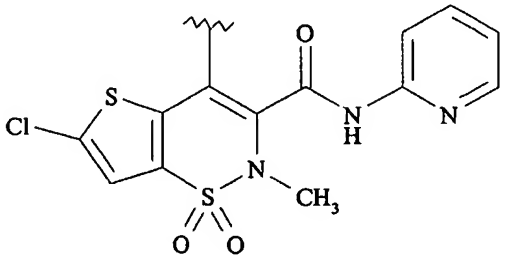












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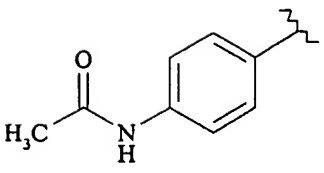
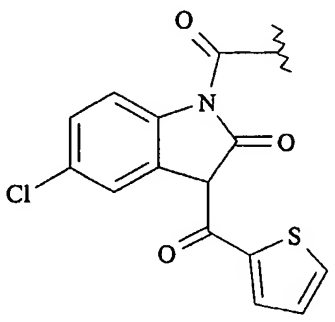
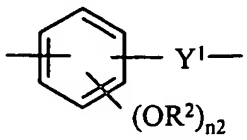


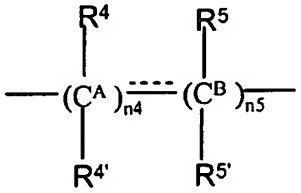


2. Use of compounds of formula (I) or salts thereof according to claim 1 wherein s is 2, c0, R, T_1, T_B, T_{B1} T_C and Y are as defined in claim 1, X_2 is



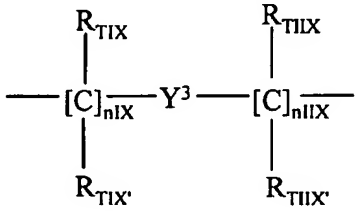
wherein:

Y^1 is $-CH_2-CH_2-(CH_2)_{n2'}-$ or $-CH=CH-(CH_2)_{n2'}-$, wherein n2' is an integer from 0 to 10, n2 is an integer 0 or 1and R^2 is H or CH_3; or



wherein

n4 is an integer from 1 to 20 and n5 is an integer from 0 to 20, R^4 and $R^{4'}$ R^5 and $R^{5'}$ are independently selected from H, CH_3, OH, NH_2, $NHCOCH_3$, COOH; when the bond between the C^A and C^B carbons is a double bond R^4 and R^5 or R4' and R^5 are absent; or



(III^p)

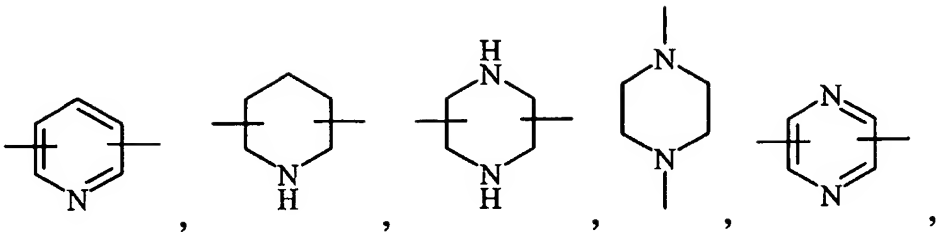
wherein

nIX is an integer from 0 to 10;

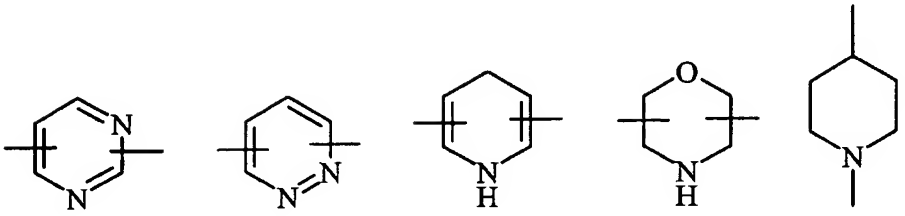
nIIX is an integer from 1 to 10;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H;

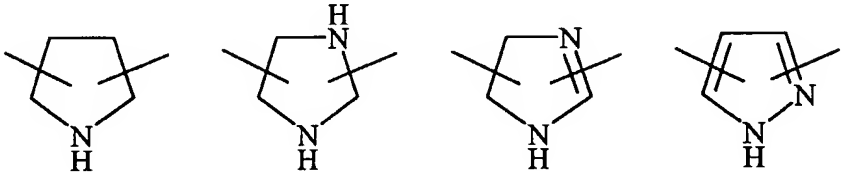
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring having 5 or 6 atoms, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, and selected from:



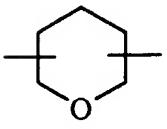
(Y1) (Y2) (Y3) (Y4) (Y5)



(Y6) (Y7) (Y8) (Y9) (Y10)

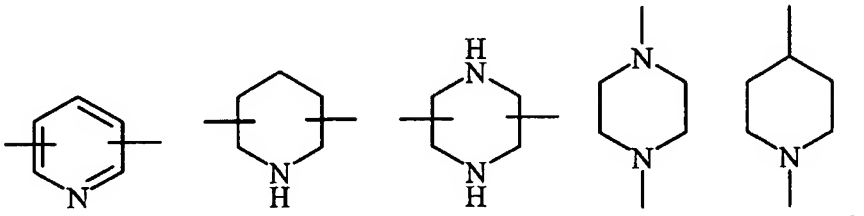


(Y11) (Y12) (Y13) (Y14)



(Y15)

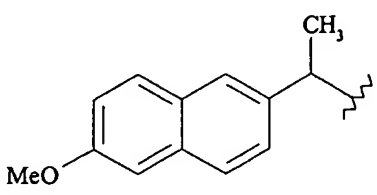
3. Use of compounds of formula (I) or salts thereof according to claim 2 wherein Y^3 is



(Y1) (Y2) (Y3) (Y4) (Y10)

Y is an alkylenoxy group –R'O- wherein R' is linear or when possible branched C_2–C_6 alkylene.

4. Use of compounds of formula (I) or salts thereof according to claim 3 wherein R is



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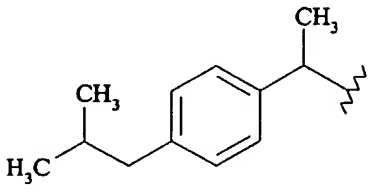

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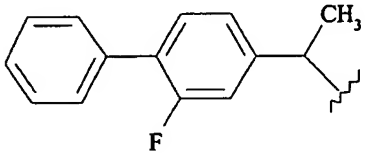

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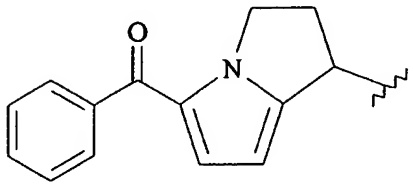

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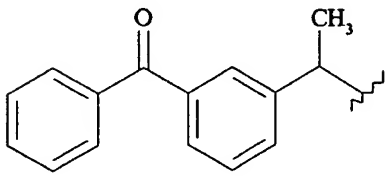

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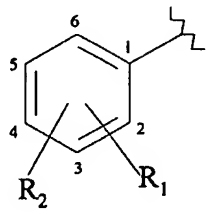
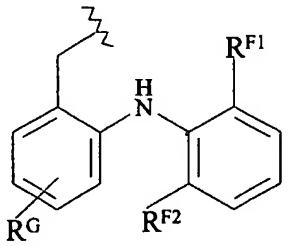


(Ia)

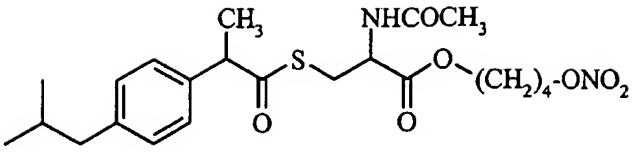


(IIa)

wherein in formula (Ia) R_1 is $-OCOCH_3$ in position 2 and R_2 is hydrogen;
wherein in formula (IIa) R^{F1} and R^{F2} are Cl or F or Br and R^G is hydrogen or methyl.

5. Use of compounds of formula (I) or salts thereof according to claims 2-4 wherein the compounds are selected from the following:

(S)-N-acetyl-[α-methyl-4-(2-methylpropyl)benzeneacetyl] ysteine 4 -nitrooxybutyl ester:



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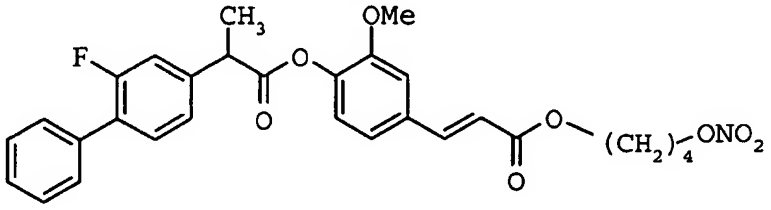
(IV^C)

trans–3–[4–[2–fluoro–α–methyl(1,1'–biphenyl)–4–acetyloxy]–3–methoxyphenyl]–2–propenoic acid 4–(nitrooxy)butyl ester:



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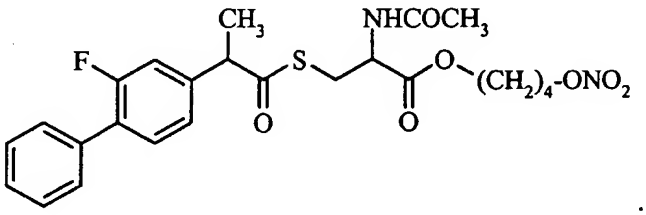
(VI^C)

(S)–N–acetyl–[2–fluoro–α–methyl(1,1'–biphenyl)–4–acetyl]cysteine 4–(nitrooxy)butyl ester:



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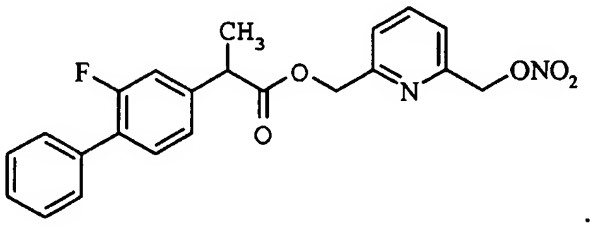
($VIII^C$)

2–fluoro–α–methyl[1,1'–biphenyl]–4–acetic acid 6–(nitrooxymethyl)–2–methylpyridyl ester:



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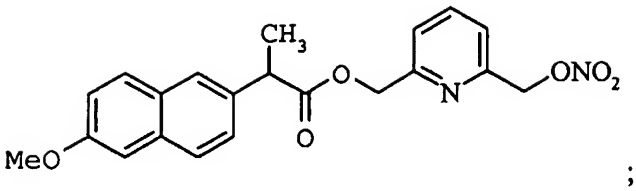
(XI^C)

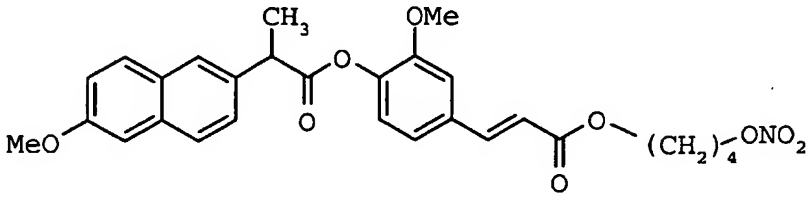
(S)–6–methoxy–α–methyl–2–naphtaleneacetic acid 6–(nitrooxymethyl)–2–methylpyridyl ester:



;

(XII^C)

trans–3–[4–[6–methoxy–α–methyl–2–naphtaleneacetyloxy]–3–methoxyphenyl]–2–propenoic acid 4 – (nitrooxy)butyl ester:



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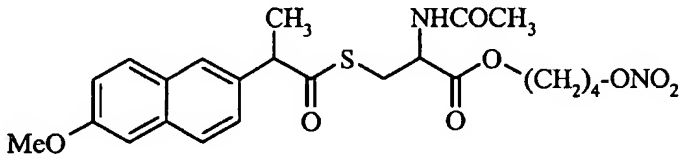
(XIII^C)

(S,S)–N–acetyl–S–(6–methoxy–α–methyl–2–naphtaleneacetyl)cysteine 4–(nitrooxy)butyl ester:



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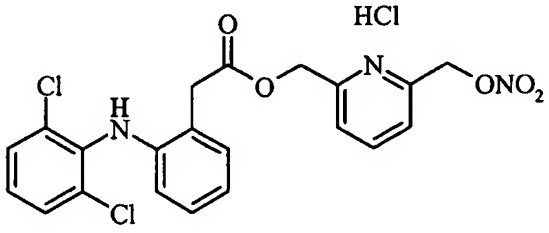
(XIV^C)

2–[(2,6–dichlorophenyl)amino]benzene acetic acid 6–(nitrooxymethyl)–2–methylpyridyl ester hydrochloride:



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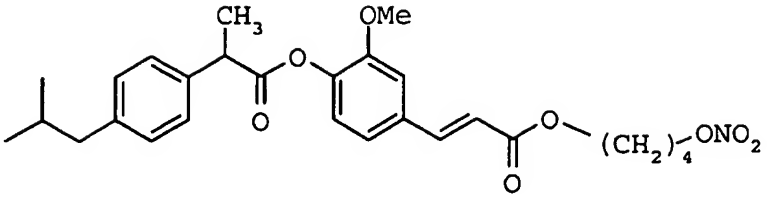
(XVI^C)

trans–3–[4–α–methyl–4–(2–methylpropyl)benzoyl acetate]–3–methoxyphenyl]-2–propenoic acid 4–(nitrooxybutyl) ester:



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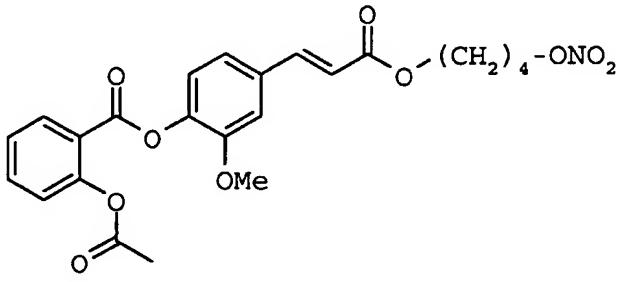
(XVII^C)

trans–3–[4–acetylbenzoyloxy]–3–methoxyphenyl]-2–propenoic acid 4–(nitrooxybutyl) ester:



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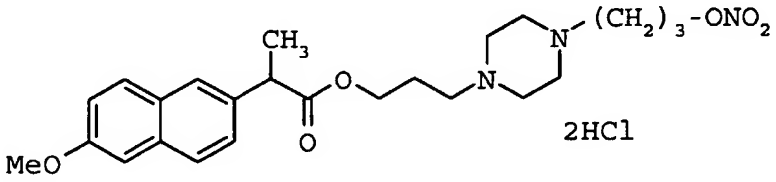
(XVIII^C)

(S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



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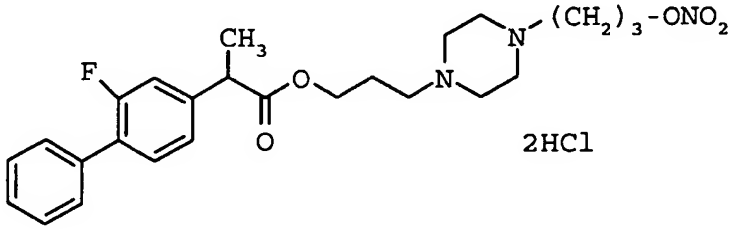
(XIX^C)

2–fluoro–α–methyl–[1,1'–biphenyl]–4–acetic acid-3-[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



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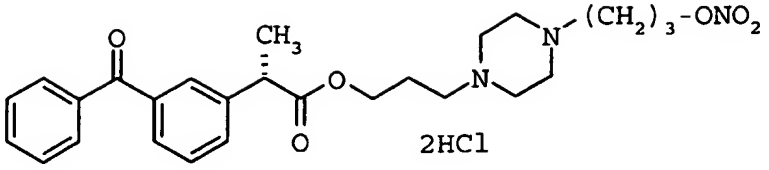
(XX^C)

(S)–3–enzoyl–α–methyl–benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



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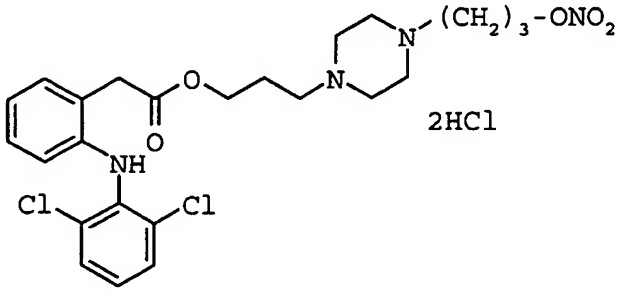
(XXI^C)

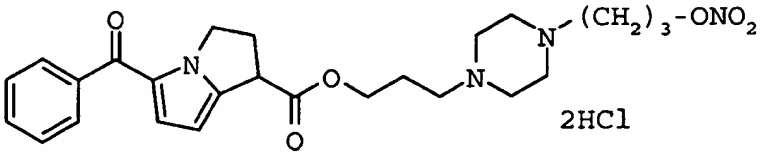
2–[(2,6–dichlorophenyl)amino]benzeneacetic acid–3-[4–(3–nitrooxypropyl)–1–piperzinyl]propyl ester dihydrochloride:



;

(XXII^C)

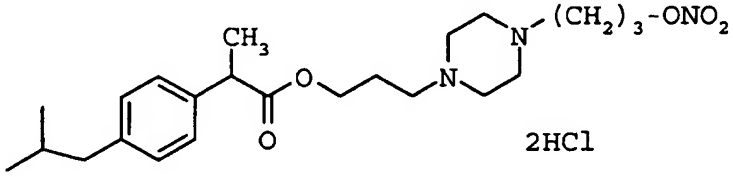
5–benzoyl–2,3–dihydro–3H–pyrrole[1,2–a]pyrrole–1–carboxylic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



;

(XXIII^C)

α–methyl–4–(2–methyl–propyl)benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



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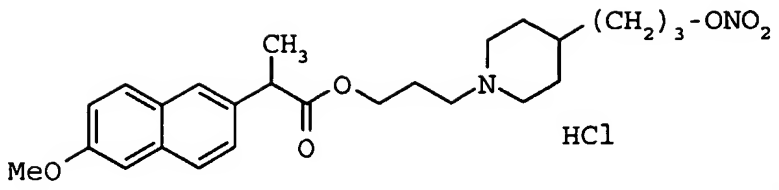
(XXIV^C)

(S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–nitroxypropyl)–1–piperidinyl]propyl ester hydrochloride:



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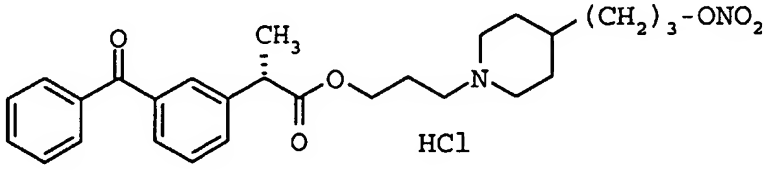
(XXV^C)

(S)–3-benzoyl–α–methyl–benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperidinyl]propyl ester hydrochloride:



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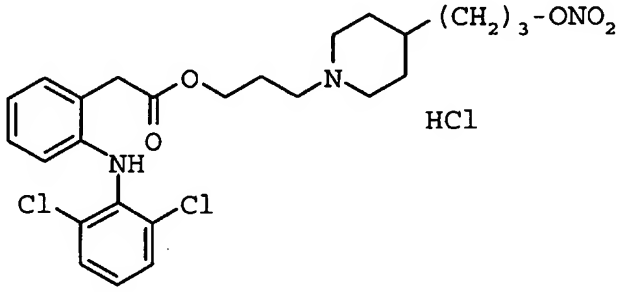
(XXVI^C)

2–[(2,6–dichlorophenyl)amino]benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperidinyl]propyl ester hydrochloride:



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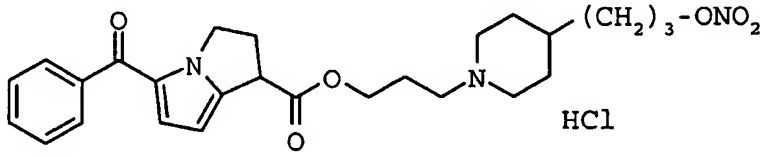
(XXVII^C)

5–benzoyl–2,3–dihydro–3H–pyrrole[1,2–a]pyrrole–1-carboxylic acid–3–[4–(3–nitrooxypropyl)–1–piperidinyl]propyl ester hydrochloride:

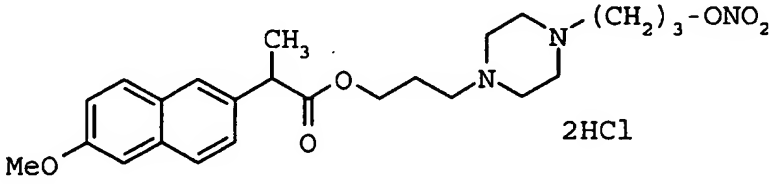


(XXVIII^C)

6. Use of compounds of formula (I) or salts thereof according to claims 1-5 for treating diseases having an inflammatory origin, osteoarthritis, arthritis, pain, fever, and for the treatment or the prevention of disorders resulting from elevates levels of COX-2.

7. Compounds of formula (I) or salts thereof according to claims 2-4 having formulas:

(S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



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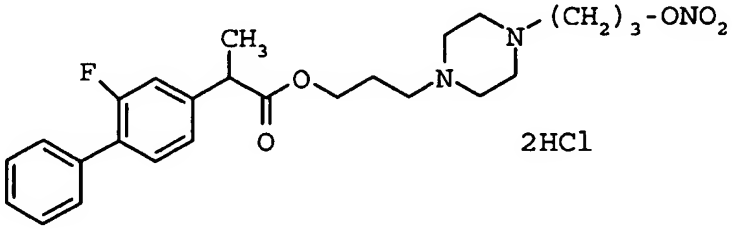
(XIX^C)

2–fluoro–α–methyl–[1,1'–biphenyl]–4–acetic acid-3-[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



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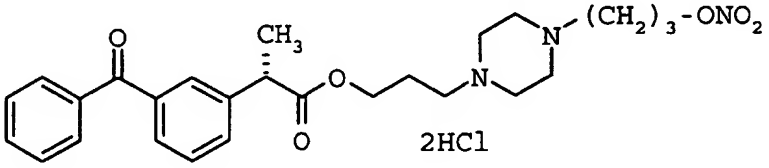
(XX^C)

(S)–3–enzoyl–α–methyl–benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



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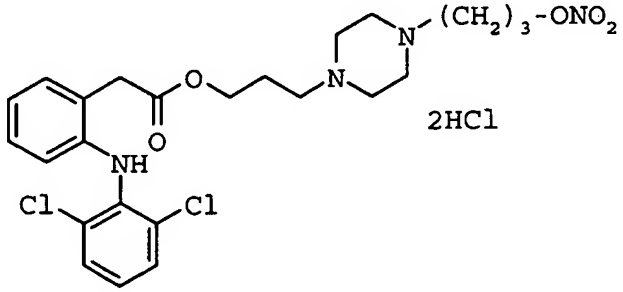
(XXI^C)

2–[(2,6–dichlorophenyl)amino]benzeneacetic acid–3-[4–(3–nitrooxypropyl)–1–piperzinyl]propyl ester dihydrochloride:



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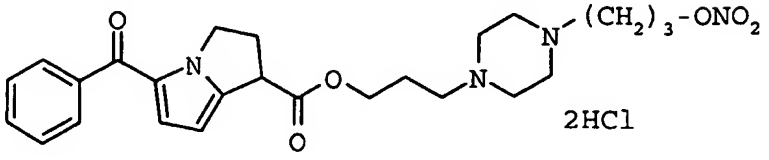
(XXII^C)

5–benzoyl–2,3–dihydro–3H–pyrrole[1,2–a]pyrrole–1–carboxylic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



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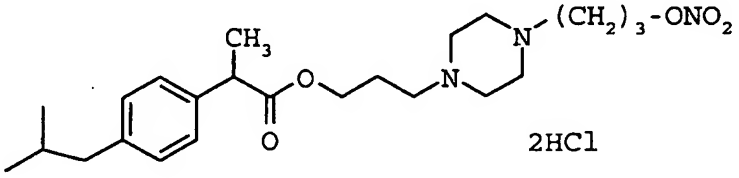
(XXIII^C)

α–methyl–4–(2–methyl–propyl)benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperazinyl]propyl ester dihydrochloride:



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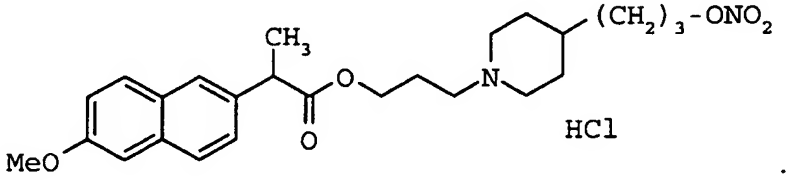
(XXIV^C)

(S)–6–methoxy–α–methyl–2–naphtaleneacetic acid–3–[4–(3–nitroxypropyl)–1–piperidinyl]propyl ester hydrochloride:



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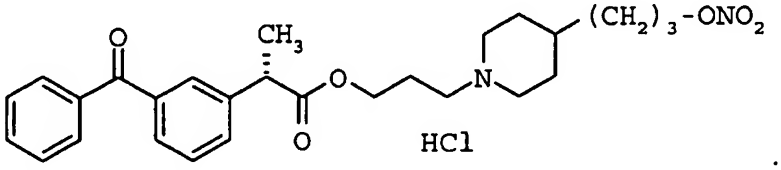
(XXV^C)

(S)–3-benzoyl–α–methyl–benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperidinyl]propyl ester hydrochloride:



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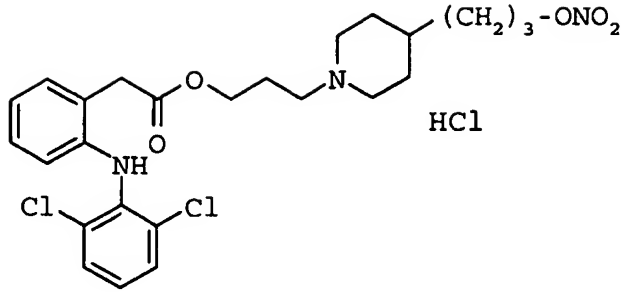
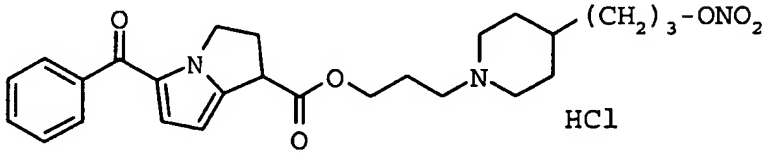
(XXVI^C)

2–[(2,6–dichlorophenyl)amino]benzeneacetic acid–3–[4–(3–nitrooxypropyl)–1–piperidinyl]propyl ester hydrochloride:



(XXVII^C)

5–benzoyl–2,3–dihydro–3H–pyrrole[1,2–a]pyrrole–1-carboxylic acid–3–[4–(3–nitrooxypropyl)–1–piperidinyl]propyl ester hydrochloride:



(XXVIII^C)

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of general formula (I) or a salt thereof according to claims 1-5.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06651

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/21 A61K31/44 A61K31/445 A61K31/496 A61K31/621
A61P19/02 A61P25/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 30866 A (NICOX SA ;ANTOGNAZZA PATRIZIA (IT); DEL SOLDATO PIERO (IT); BENEDI) 18 April 2002 (2002-04-18) abstract examples 1-20 claims 1-10 ---	5-8
X	WO 00 61537 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) cited in the application abstract page 1, paragraph 1 page 2 examples 1-28 claims 1-10 --- -/--	5-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2003	13/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Taylor, G.M.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 51988 A (NICOX SA ;DEL SOLDATO PIERO (IT); BENEDINI FRANCESCA (IT)) 8 September 2000 (2000-09-08) cited in the application abstract page 1 examples 1-15 claims 1-14	5-8
X	JANTZEN, P T ET AL.: "Microglial Activation and beta-Amyloid Deposit Reduction Caused by a Nitric Oxide-Releasing Nonsteroidal Anti-Inflammatory Drug in Amyloid Precursor Protein Plus Presenilin-1 Transgenic Mice" JOURNAL OF NEUROSCIENCE, vol. 22, no. 6, 15 March 2002 (2002-03-15), pages 2246-2254, XP002255826 abstract	5-8
A	WO 00 61541 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) cited in the application abstract page 1 -page 2 examples 1-20 claims 1-10	5-8
A	WO 95 30641 A (NICOX LTD ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 (1995-11-16) cited in the application abstract page 1 examples 1,2 table 4 claims 1-7	5-8
P,A	WO 02 100400 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 December 2002 (2002-12-19) abstract page 1 -page 2 claims 1-6	5-8

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4, 5(part), 6(part)

Present claims 1-4 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Notwithstanding the above, present claims 1-6 relate to a product defined by reference to a desirable characteristic or property, namely, "the treatment or prevention of disorders resulting from elevated leverls of COX-2", and "COX-2 inhibitor drugs".

The claims cover all diseases having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such diseases. Moreover, the Applicant has not provided any test to determine whether any given disease falls within this definition, and none is available in the prior art. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products defined in claims 5, 7 and 8, for the treatment of the specific diseases mentioned in claim 6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/06651

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-4, 5(part), 6(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ıation on patent family members

International Application No
PCT/EP 03/06651

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0230866	A	18-04-2002	IT	MI20002202 A1	12-04-2002
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INTERNATIONAL SEARCH REPORT

ıation on patent family members

International Application No
PCT/EP 03/06651

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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